

**REMARKS**

**STATUS OF THE CLAIMS**

Claims 1-9, 11 and 12 are pending. Claim 12 is withdrawn from consideration.

Claims 1-9 and 11 are under consideration.

**REJECTIONS UNDER 35 U.S.C. § 103**

**(A) Rejection of Claims 1, 3-6 and 9**

In this Office Action, at item 7 on page 4, claims 1, 3-6, and 9 are rejected under 35 U.S.C. §103(a) as being unpatentable over by Caillat et al (European Patent Application Publication No. EP 0 882 981 A1, published 12 September 1998) ("Caillat") in view of Hashimoto et al (U.S. Patent No 5,776,672, issued 7 July 1997) ("Hashimoto"), and, as applied to claim 5, as evidenced by the online dictionary at [dictionary.cambridge.org](http://dictionary.cambridge.org), and, as applied to claim 9, as evidenced by the online dictionary at [Merriam-Webster.com](http://Merriam-Webster.com). Citations of Caillat et al are from U.S. Patent 6,126,800, which is an English language equivalent of the European Patent Application.

The Examiner alleges that Caillat teaches a detection chip having a depression, namely a cuvette, DNA encompassing gene samples, and the measurement of an electric current variation. The Examiner asserts that the various "uses" recited in claim 1 "fail to define additional structural elements to the device" and therefore the claim is obvious over Caillat.

However, the Examiner admits that Caillat does not teach that the immobilized oligonucleotides as part of the chip, and that the electrodes are for detecting point mutation. Nevertheless, the Examiner argues that Hashimoto teaches electrodes having single stranded nucleic acid probes immobilized thereon that are capable of detecting "an extremely small amount of analyte." As a result, the Examiner concludes that it would have been obvious to one having ordinary skill in the art to modify the detection chip according to Caillat by combining the teaching according to Hashimoto's immobilized oligonucleotides to arrive at the claimed invention.

Applicants respectfully disagree with the Examiner, particularly in light of the current

amendment. In this amendment, claim 1 is now amended to recite at least the following features:

- (a) a plurality of terminals, each being connected to a corresponding measuring electrode,
- (b) a common electrode having a terminal,
- (c) when a voltage is applied between the terminal of the common electrode and the plurality of terminals of measuring electrodes, an electric current is generated and measured,
- (d) a voltage is applied before hybridization, generating a current before hybridization,
- (e) a voltage is applied after hybridization, generating a current after hybridization, and
- (f) the variation between the current before hybridization and the current after hybridization depends on the number of mismatched DNA pairs and therefore a single base substitution SNP or point mutation of genes can be detected.

As a result of the amendment, amended claim 1 is not obvious over Caillat because Caillat does not teach or suggest about hybridization or about the variation between the current before hybridization and the current after hybridization. The major emphasis in Caillat is the use of fluorescence as the method of detection. Caillat's apparent teaching that "measurement current can be selectively measured between a given analysis electrode and the counter electrode" (Caillat, column 6, lines 15-21) is far from being a teaching or suggestion for the invention in amended claim 1. By virtue of only such a suggestion in Caillat, one having ordinary skill in the art would not have been able to arrive at the claimed invention according to amended claim 1.

Furthermore, Hashimoto teaches the use of a "double stranded nucleic acid recognizing substance capable of binding specifically to the double stranded nucleic acid and being active electrochemically or optically" (Hashimoto, Abstract, lines 8-11). In Example 30 of Hashimoto, the DNA "recognizing substance" is "acridine orange" (Hashimoto, column 53, lines 48-50), which is the DNA "recognizing substance capable of binding specifically to the double stranded" DNA. The use of acridine orange leads to a change of the appearance of a box according to FIG. 9 of Hashimoto, which is feasible because fluorescence is the basis of the detection in Hashimoto. Further explanation of such an approach of detection is illustrated in FIG. 10 of Hashimoto.

In contrast, according to this application, there are several problems related to the use of fluorescence (U.S. Publication 2004/0185462, ("the '462 Publication"), Paragraphs [0009] – [0010]). Because the number of single base substitution SNP of genes or point mutation of genes is immense, "it is almost impossible to exhaustively analyze single base substitution and

point mutation" if conventional methods involving fluorescence are used (the '462 Publication, Paragraph [0011]). Therefore, to solve the problems related to the conventional method, this application uses a different approach to detecting and analyzing single base substitution SNP and point mutation (the '462 Publication, Paragraph [0012]).

Therefore, Hashimoto teaches away from the invention of amended claim 1 because Hashimoto uses a method that the invention of amended claim 1 intends to avoid. As such, the teaching or suggestion in Hashimoto would not have been helpful to one having ordinary skill in the art to combine with the teaching or suggestion according to Caillat to arrive at the invention in amended claim 1. Therefore, amended claim 1 would not have been obvious over Caillat and Hashimoto, alone, or as a combination.

Because independent amended claim 1 is patentable over Caillat and Hashimoto, claims 3-6 and 9, which are dependent from amended claim 1, should also be patentable over Caillat and Hashimoto.

Therefore, the rejection of claims 1, 3-6 and 9 under 35 U.S.C. §103 as obvious over Caillat and Hashimoto should be withdrawn.

(B) Rejection of Claims 2 and 11

In this Office Action, at item 8 on page 8, claims 2 and 11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Caillat et al ("Caillat") in view of Hashimoto et al ("Hashimoto") as applied to claim 1 above, and further in view of Wilding et al (U.S. Patent No. 5,587,128, issued 24 December 1996) ("Wilding").

The Examiner admits that neither Caillat nor Hashimoto teaches injection holes extending through the body and the cover into said depression. However, the Examiner alleges that Wilding teaches a device for "detecting polynucleotides" by measuring conductivity (Wilding, column 21, lines 15-20). The Examiner also alleges that Wilding teaches injection holes (FIG. 1C, Part 16), although Wilding does not teach that the injection holes are on "two opposing surfaces of each of said body and said cover." The Examiner concludes that it would have been obvious to one having ordinary skill in the art to have modified the chip of Caillat in view of Hashimoto to have injection holes extending through the body and the cover as taught by Wilding.

Applicants respectfully disagree with the Examiner because Wilding is directed to a device to amplify a nucleotide by conducting a polynucleotide amplification reaction inside a mesoscale reaction chamber. The teaching of Wilding does not make the invention according to

amended claim 1 obvious.

In contrast, amended claim 1 of the application recites a number of features, including at least: (a) a plurality of terminals, each being connected to a corresponding measuring electrode, (b) a common electrode having a terminal, (c) when a voltage is applied between the terminal of the common electrode and the plurality of terminals of measuring electrode, a current can be generated, and (d) the variation of the current generated before hybridization and the current generated after hybridization will be indicative of point mutation of genes.

Therefore, as noted above already, amended claim 1 would not have been obvious over the teaching or suggestion of Caillat and Hashimoto. Furthermore, even if the teaching of Wilding is allowed to be combined with that of Caillat and Hashimoto, one having ordinary skill in the art would not have been able to modify the teaching of Caillat and Hashimoto by the prompting of the teaching of Wilding to arrive at the invention according to amended claim 1. The teaching of the use of fluorescence according to Caillat and Hashimoto could not be modified by the teaching of mesoscale polynucleotide amplification device according to Wilding to arrive at the detection of point mutation in genes using a current generated before hybridization and a current generated after hybridization as recited in amended claim 1. Therefore amended claim 1 is not obvious over Caillat, Hashimoto, and Wilding, alone or as a combination.

Because independent amended claim 1 is patentable over Caillat, Hashimoto and Wilding, claims 2 and 11, being dependent from amended claim 1, should also be patentable over Caillat, Hashimoto and Wilding.

Therefore, the rejection of claims 2 and 11 under 35 U.S.C. §103 as obvious over Caillat, Hashimoto, and Wilding should be withdrawn.

(C) Rejection of Claim 7

In this Office Action, at item 9 on page 12, claim 7 is rejected under 35 U.S.C. §103(a) as being unpatentable over by Caillat et al ("Caillat") in view of Hashimoto et al ("Hashimoto") as applied to claim 1 above, and further in view of Heller et al (U.S. Patent No. 5,632,957, issued 27 May 1997) ("Heller").

The Examiner admits that neither Caillat nor Hashimoto teaches one-to-one wiring. However, the Examiner alleges that Heller teaches a chip comprising different nucleic acids attached to each of a plurality of microlocations (Heller, column 4, lines 55-60) wherein each of the plurality of microlocations has an electrodes that are measuring electrodes. The Examiner

concludes that it would have been obvious to one having ordinary skill in the art to modify the chip of Caillat in view of Hashimoto so that the chip comprises the one-to-one wiring taught by Heller.

Applicants respectfully disagree with the Examiner because Heller does not teach or suggest at least the following features recited in amended claim 1:

- (a) a common electrode having a terminal,
- (b) when a voltage is applied between the terminal of the common electrode and the plurality of terminals of measuring electrodes, an electric current is generated and measured,
- (c) a voltage is applied before hybridization, generating a current before hybridization,
- (d) a voltage is applied after hybridization, generating a current after hybridization, and
- (e) the variation between the current before hybridization and the current after hybridization depends on the number of mismatched DNA pairs and therefore a single base substitution SNP or point mutation of genes can be detected.

Therefore, amended claim 1 would not have been obvious over Heller alone. Also, as noted above already, amended claim 1 would not have been obvious over the teaching or suggestion of Caillat and Hashimoto. Furthermore, even if the teaching of Heller is allowed to be combined with that of Caillat and Hashimoto, one having ordinary skill in the art would not have been able to modify the teaching of Caillat and Hashimoto by the prompting of the teaching of Heller to arrive at the invention according to amended claim 1. The teaching of the use of fluorescence according to Caillat and Hashimoto could not be modified by the teaching of the one-to-one wiring taught by Heller to arrive at the detection of point mutation in genes using a current generated before hybridization and a current generated after hybridization as recited in amended claim 1. Therefore amended claim 1 would not have been obvious over Caillat, Hashimoto, and Heller, alone or as a combination.

Because independent amended claim 1 is patentable over Caillat, Hashimoto and Heller, claim 7, being dependent from amended claim 1, should also be patentable over Caillat, Hashimoto and Heller.

Therefore, the rejection of claim 7 under 35 U.S.C. §103 as obvious over Caillat, Hashimoto, and Heller should be withdrawn.

(D) Rejection of Claims 8-9

In this Office Action, at item 10 on page 14, claims 8-9 are rejected under 35 U.S.C. §103(a) as being unpatentable over by Caillat et al ("Caillat") in view of Hashimoto et al

("Hashimoto") as applied to claim 1 above, and further in view of Wohlstadter et al (PCT International Application Publication No. WO 98/12539, published 26 March 1998) ("Wohlstadter")

The Examiner admits that neither Caillat nor Hashimoto teaches a measuring apparatus in which the chip becomes electrically connected and which measures a current or that the chip is configured to be an insertable cassette. However, the Examiner argues that Wohlstadter teaches a chip comprising measuring electrodes and counter electrodes in the form of a cassette. The Examiner concludes that it would have been obvious to one having ordinary skill in the art to modify the chip of Caillat in view of Hashimoto by using the teaching of Wohlstadter so that the chip can be made to be an insertable cassette.

Applicants respectfully disagree with the Examiner because Wohlstadter does not teach or suggest at least the following features that are recited in amended claim 1:

- (a) when a voltage is applied between the terminal of the common electrode and the plurality of terminals of measuring electrodes, an electric current is generated and measured,
- (b) a voltage is applied before hybridization, generating a current before hybridization,
- (c) a voltage is applied after hybridization, generating a current after hybridization, and
- (d) the variation between the current before hybridization and the current after hybridization depends on the number of mismatched DNA pairs and therefore a single base substitution SNP or point mutation of genes can be detected.

Wohlstadter teaches the use of a cassette for conducting electrochemiluminescence ("ECL") (Wohlstadter, page 6, lines 9-11). Wohlstadter specifically teaches the use of a labeled compound capable of electrochemiluminescence (Wohlstadter, page 219, lines 4-5), the use of a voltage to induce the label to luminesce, and the detection of the emitted luminescence. Therefore, Wohlstadter teaches away from the invention by involving a labeled compound capable of electrochemiluminescence. In addition, the signal to be detected in Wohlstadter is "emitted luminescence," not a current generated before hybridization and a current generated after hybridization and the use of the variation of the current as a detection of point mutation of genes as recited in amended claim 1. Therefore, amended claim 1 would not have been obvious over Wohlstadter.

As noted above already, amended claim 1 would not have been obvious over the teaching or suggestion of Caillat and Hashimoto. Furthermore, even if the teaching of Wohlstadter is allowed to be combined with that of Caillat and Hashimoto, one having ordinary skill in the art would not have been able to modify the teaching of Caillat and Hashimoto by the prompting of the teaching of Wohlstadter to arrive at the invention according to amended claim

1. The teaching of the use of fluorescence according to Caillat and Hashimoto could not be modified by the teaching of using an insertable cassette taught by Wohlstadter to arrive at the detection of point mutation in genes using a current generated before hybridization and a current generated after hybridization as recited in amended claim 1. Therefore amended claim 1 would not have been obvious over Caillat, Hashimoto, and Wohlstadter, alone or as a combination.

Because independent amended claim 1 is patentable over Caillat, Hashimoto and Wohlstadter, claims 8 and 9, being dependent from amended claim 1, should also be patentable over Caillat, Hashimoto and Wohlstadter.

Therefore, the rejection of claims 8 and 9 under 35 U.S.C. §103 as obvious over Caillat, Hashimoto and Wohlstadter should be withdrawn.

### CONCLUSION

If there are any formal matters remaining after this response, the Examiner is requested to telephone the undersigned to attend to these matters.

If there are any additional fees associated with filing of this Amendment, please charge the same to our Deposit Account No. 19-3935.

Respectfully submitted,

STAAS & HALSEY LLP

Date: November 12, 2008

By: David K. Ho  
David K. Ho  
Registration No. 53,025

1201 New York Ave, N.W., 7th Floor  
Washington, D.C. 20005  
Telephone: (202) 434-1500  
Facsimile: (202) 434-1501